REMARKS

Claims 1, 53, 54, 57, 59, and 60 are pending and rejected under 35 U.S.C. 103(a); claims 2-52, 55-56, 58, and 61-119 are cancelled; new claims 120-122 have been added. Each of the rejections is addressed below.

Support for the Amendments

Support for new claims 120, 121, and 122 is found at original claims 22, 23, and 24, respectively. No new matter has been added.

Rejections under 35 U.S.C. 103(a)

Claims 1, 53, 54, 57, 59 and 60 are rejected under 35 U.S.C. 103(a) as obvious over Pausch et al. WO 95/21925 (hereinafter "Pausch"), Conklin et al., *Molecular Pharmacology* 50:885-890, 1996 (hereinafter "Conklin"), Brown et al., WO 99/14344, (hereinafter "Brown"), and/or Fowlkes et al. WO 94/23025 (hereinafter "Fowlkes"), in view of Hamm et al., *Journal of Biological Chemistry* 273:669-672. Applicants respectfully disagree and traverse the rejection.

Claims 1, 53, 54, and 57 are directed to recombinant yeast cells expressing a heterologous G protein-coupled receptor (GPCR) in the cell membrane of the yeast cell, such that signal transduction activity via the receptor is modulated by interaction of an extracellular region of the receptor with an extracellular signal, and a chimeric G protein subunit comprising an endogenous yeast Gpa1 subunit in which at least the last four C-terminal amino acids of Gpa1 are replaced with at least the last four C-terminal amino acids of a first heterologous G protein subunit, and in which at least the first five N-terminal amino acids of Gpa1 are replaced with at least the first five N-terminal amino acids of a second heterologous G protein subunit; and claims 59 and 60 are directed to chimeric G protein subunits that contain an endogenous Gpa1 subunit where the last four C-terminal amino acids of Gpa1 are replaced with at least the last four C-terminal amino acids of a heterologous G protein subunit, and the N-terminus of Gpa1 is operably linked to at least the first five N-terminal amino acids of a second heterologous G protein subunit.

The Examiner asserts that Pausch, Fowlkes, Brown, and Conklin describe chimeric G proteins that differ from the claimed invention only in the N-terminus. The Examiner further asserts that it would have been obvious to modify the chimeric G protein subunits described by the references to substitute the first five N-terminal amino acids of the protein with amino acids

from a second heterologous protein in view of Hamm, which provides a review of the structure and role of G protein-coupled receptors. For the reasons described below, Applicants disagree with the rejection and request that it be withdrawn.

The test of obviousness requires that one compare the claimed "subject matter as a whole" with the prior art "to which said subject matter pertains" 35 U.S.C. § 103(a). To establish a *prima facie* case of obviousness, three criteria must be met. First, a suggestion or motivation to modify the reference or combine reference teachings must be present in the references or in the general knowledge present in the art. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. M.P.E.P. 2143. The burden is on the Examiner to show that the references expressly or impliedly suggest all of the claim limitations. M.P.E.P. 2142. "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons skilled in the art." *In re Rouffet*, 149 F.3d 1350, 1357. In the absence of some teaching or suggestion to combine, no *prima facie* case of obviousness can be established, and the rejection is improper and must be withdrawn. *In re Fine*, 837 F.2d 1071, 1074.

In the present case, the references cited by the Examiner fail to provide the requisite motivation to combine; fail to provide a reasonable expectation of success; and fail to teach or suggest all of the claim limitations. Each of the references cited by the Examiner in support of the obviousness rejection is considered below.

Pausch

Pausch describes chimeric Gα proteins having yeast Gα (Gpa1p) amino acid sequences fused to a second heterologous G protein (page 14, lines 17-20). In particular, Pausch describes the fusion of the amino terminal domain of Gpa1 with the ***carboxy terminal domain*** of a heterologous $G_{\alpha 1}$, $G_{\alpha s}$, and $G_{\alpha i2}$ (page 14, lines 17-20). As acknowledged by the Examiner, Pausch neither teaches nor suggests modifying the N-terminus of Gpa1p to include at least the first five N-terminal amino acids of a second heterologous G protein subunit.

Conklin

Conklin describes chimeric G protein subunits having ***C-terminal modifications***. Conklin fails to teach or suggest modifying the N-terminus of such proteins. In fact, Conklin focuses exclusively on carboxyl terminal mutations because the C-terminus was widely recognized as important for receptor coupling as evidenced in the prior art cited by Conklin (page 885, paragraph 1). Conklin states that "[t]he carboxyl terminus of the G protein α subunit is a ***key determinant*** of the fidelity of receptor activation." (page 885, left column, Summary; emphasis added.)

Although Conklin teaches that the C terminus is a particularly attractive region for mutagenesis, Conklin fails to teach or suggest the introduction of mutations in the N-terminus of a Gα subunit, much less Applicants' claimed chimeric G proteins, which require that the N-terminus of Gpa1 be operably linked to at least the first five N-terminal amino acids of a second heterologous G protein subunit.

Brown

Like Conklin, Brown describes chimeric Gα proteins having ***modifications within the C-terminus***, exclusively (page 4, line 18, to page 5, line 6). Brown's production of C terminal modifications provides chimeric G proteins that are "unexpectedly" efficient in coupling mammalian seven transmembrane receptors to the yeast mating pathway (page 4, lines 13-16). Brown states:

> Moreover, we have found that the approach of substituting the five C-terminal amino acids of Gpa1p to generate the transplants is widely applicable, in that we have generated transplants of representative members of all four Gα families: Gαi, Gαs, GαQ, and Gα12. ***This was not possible in previously described approaches*** to chimera expression. . . Lastly, the pheromone response pathway is not activated in cells which express integrated versions of the transplants in the absence of activated receptors. This indicates that manipulations to the C-terminal amino acids do not interfere with the interaction with Gß/Gγ; ***this was not true with previously described approaches*** to chimera construction. (page 7, line 28, to page 8, line 6; emphasis added.)

In view of the prior art, Brown suggests that the functional success of chimeric Gα subunits having C terminal modifications was suprising. Given the "unexpected" success of Brown's

approach in modifying the C terminus, one would lack the requisite expectation of success to modify the N-terminus. Furthermore, Brown, like Conklin and Pausch, fails to teach or suggest all of the limitations of Applicants' claimed invention. Specifically, Brown fails to teach or suggest that the N-terminus of Gpa1 be operably linked to at least the first five N-terminal amino acids of a second heterologous G protein subunit.

Fowlkes

Fowlkes describes chimeric Gα proteins having a variety of modifications (page 43, lines 36, to page 44, line 16). The Examiner asserts that Fowlkes differs from the claimed invention and does not teach or suggest a chimeric G proteins, where the N-terminus of Gpa1 is coupled to at least the first five N-terminal amino acids of a second heterologous G protein subunit.

Hamm

None of the foregoing references describes each and every limitation of Applicants' claimed invention, and none provides the requisite motivation to couple the N-terminus of Gpa1 to at least the first five N-terminal amino acids of a second heterologous G protein subunit. The Examiner relies on Hamm to supply the motivation that is uniformly missing in Pausch, Fowlkes, Brown and Conklin. Specifically, the Examiner states:

> Accordingly, the Hamm reference would provide motivation to one of ordinary skill in the art at the time of applicant's invention to further modify the chimeric Gα protein subunits obtained by the Pausch, Fowlkes, Brown and Conklin references by linking or substituting into the N terminal portion of the reference chimeras corresponding heterologous amino acids in order to obtain sandwich chimeras (e.g. N-term heterologous-GPA1-C terminal heterologous) that can be screened for different degrees (e.g. increased/decreased) of heterologous receptor coupling. (Office Action, page 7, second full paragraph.)

Contrary to the Examiner's assertion, Hamm fails to teach or suggest modifying the N-terminus of Gpa1, such that it is coupled to at least the first five N-terminal amino acids of a second heterologous G protein subunit. Hamm merely provides a review of G protein-coupled receptor signaling. Hamm entirely fails to teach or suggest the introduction of ***any*** mutation into

a Gα subunit, much less the specific mutations of the presently claimed invention. In the absence of such a teaching or suggestion, the Examiner has failed to establish a *prima facie* case of obviousness.

Furthermore, like Pausch, Fowlkes, Brown and Conklin, which focus exclusively on modifying the C terminus, Hamm teaches that residues at the C terminus are critical for mediating G protein coupled receptor interactions. Although Hamm acknowledges that the N-terminal region is "implicated" in receptor contact (page 669, right column, 4th paragraph), Hamm states:

> On the α subunit, ***the best characterized receptor contact region is at the C terminus***. The last 7 amino acids of the α subunit are disordered in the heterotrimer crystal structures, and analysis of receptor-binding peptides selected from a combinatorial peptide library shows that ***these 7 residues are the most critical***. Studies using chimeric Gα subunits confirm that in fact ***the last 5 residues contribute importantly to specificity of receptor G protein interaction***. Elegant mutagenesis studies have shown that the C terminus of the third intracellular loop of receptors binds to ***this C-terminal region on Gα subunits***. (p. 669, third paragraph, Emphasis added.)

By emphasizing the importance of the C terminus in mediating receptor contact and specificity, Hamm and the other cited references not only direct the skilled artisan's attention towards the C terminus, they teach away from modifying the N terminus of the protein. In view of this teaching away, one skilled in the art would lack the requisite motivation to introduce changes to the Gα subunit N terminus as well as any expectation of success.

Even if we accept *in arguendo* that Hamm does provide the motivation to modify the N-terminus of Gpa1, such that it is coupled to at least the first five N-terminal amino acids of a second heterologous G protein subunit, one skilled in the art would still lack the requisite expectation of success to make such a modification.

In the Office Action at page 7, second full paragraph, the Examiner states that "sandwich chimeras (e.g. N-term heterologous-GPA1-C terminal heterologous) ***can be screened*** for different degree (e.g. increased/decreased) of heterologous receptor coupling." By suggesting that each modified subunit would have to be tested, the Examiner implies that it is uncertain whether such chimeric G protein subunits would function successfully. Applicants submit that the lack of expectation of success is manifest in the Examiner's implication.

Moreover, the fact that such screening experiments could be undertaken is irrelevant. The standard in determining obviousness is not whether certain experiments ***could be tried***, but whether the prior art suggested that the claimed N-terminal modifications ***should be made***, and further suggested that proteins containing such modifications ***would function successfully***. *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir.,1988). In this case, court held:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that ***this process should be carried out*** and would have ***a reasonable likelihood of success***, viewed in the light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art not in the applicant's disclosure. *Id* at 473. (citations omitted; emphasis added.)

In the absence of a suggestion that modified subunits ***should be made***, and if made, that such subunits would function successfully, the Examiner has failed to establish a *prima facie* case of obviousness. Where the cited references fail to establish a reasonable expectation of success, the obviousness rejection is improper and should be withdrawn.

In sum, the Examiner admits that Pausch, Fowlkes, Brown and Conklin fail to describe each and every claim limitation present in Applicants' claimed invention. Specifically, the Examiner acknowledges that these references fail to teach or suggest modifying the N-terminus of Gpa1, such that it is operably linked to at least the first five N-terminal amino acids of a second heterologous G protein subunit. In addition, Pausch, Fowlkes, Brown and Conklin, which uniformly focus on the C terminus, fail to provide the motivation to introduce a modification at the N terminus of Gpa1. The Examiner relies on Hamm to provide such motivation, but this reliance is misplaced; neither Hamm nor any of the other cited references, alone or in combination, teaches or suggests modifying the N terminus of Gpa1, as required by Applicants' claims. Moreover, none provides the requisite expectation of success required to produce the claimed invention since the Examiner acknowledges that it is uncertain whether such chimeric proteins would function successfully.

Applicants also note that the Examiner relies on no less than five references in making the obviousness rejection. Applicants submit that such reliance belies the alleged obviousness of the claimed invention. *Hybritech, Inc. v. Monoclonal Antibodies*, Inc., 802 F.2d 1367, 1383 (Fed. Cir. 1986). "The large number of references, as a whole, relied upon by the district court to show obviousness, about twenty in number, skirt all around but do not as a whole suggest the

claimed invention, which they must, to overcome the presumed validity." *Id.* at 1383. While the number of references is not determinative, "the requisite prior art suggestion to combine becomes less plausible when the necessary elements can only be found in a large number of references." 2 Chisum on Patents § 5.04[1][e][vi].

The Office has failed to establish a *prima facie* case of obviousness, and the rejection of the claims under U.S.C. § 103(a) should be withdrawn.

CONCLUSION

In view of the above remarks, Applicants believes the pending application is in condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. Should any of the claims not be found to be allowable, Applicants respectfully request the Examiner to telephone Applicants' undersigned representative at the number below so that a telephonic interview may be scheduled. Applicants thank the Examiner in advance for this courtesy.

Respectfully submitted,

EDWARDS ANGELL PALMER & DODGE LLP

By _____

Melissa Hunter-Ensor, Ph.D.
Registration No.: 55,289
P.O. Box 55874
Boston, Massachusetts 02205
(617) 439-4444
Attorneys/Agents For Applicant

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